Fetal Conditions Associated with Lung Hypoplasia

Aetiology & Outcomes

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Fetal Conditions Associated with Secondary Lung Hypoplasia

Intrathoracic
- CDH
  - Diaphragmatic eventration?
- Lung masses
  - CCAM
  - BPS
- Mediastinal/cardiac masses
- Pleural effusions
- Pericardial effusions

Extrathoracic
- Oligohydramnios
  - Bilat. renal agenesis
  - Severe renal dysfunction
- LUTO
- PPROM
  - "Stuck twin"
- Skeletal dysplasias
  - small thorax
- Fetal akinesia

Pulmonary Hypoplasia

Pathological Criteria

- Lung weight: body weight ratio (LBWR)
  - Hypoplasia:
    - LBWR ≤ 0.015 < 28 wks
    - LBWR ≤ 0.012 ≥ 28 wks
- Combined lung weights > 1 SD below mean
- Mean Radial Alveolar Count (RAC)
  - indicator of histological pulmonary maturation
- Cellular elements present
- Alveolar & arteriolar wall thickness


Fetal Lung Development Stages

Type & degree of pulmonary hypoplasia dependant on stage when insult occurs

- decreased, thicker, more cellular bronchioles
- abN pulmonary vasculature
  - e.g. LUTO
  - Renal dysgenesis

Gucciardo L. Best Pract O&G 2008;12(1):123
Pulmonary Hypoplasia Prediction

• ↓ pulmonary cell numbers, air space & alveoli
• Incidence varies from 9-11/10,000 live births
• Mortality rate ~ 50–90%

• Prediction of lethal pulmonary hypoplasia pivotal to improve counseling & neonatal resuscitation

Pulmonary Hypoplasia Prediction of Severity / Outcome

• US - 2D Lung Head Ratio (LHR, o/e LHR)
  - 3D Lung volume
• MRI - volume
  - signal intensity (LLSIR)
• Branch Pulmonary Arteries
  • Size
  • Hyperoxygenation test

Fetal Lung Abnormalities

Fetal Pleural Effusions

1:10,000 - 15,000 births

Outcomes:

• Spontaneous resolution
• Pulmonary hypoplasia
• Fetal hydrops
• Death
Mechanism of hydrops in hydrothorax?

- Cardiac Tamponade
- Lung compression
- Lymphatic obstruction
- Venous resistance
- Hydropic: No treatment → 10-20% survival

Pleural effusion volume

Intra thoracic pressure

Fetal Chest Shunt Insertion

9F

Fetal Chest Shunt Insertion

University of Toronto

Fetal Chest Shunts 1992-2011

- All large pleural effusion referrals
  - n = 147
  - No other abnormality noted
  - Hydrothorax suspected as primary dx.
  - Large effusion

- Shunts 108 fetuses
  - 71% Bilateral effusions
  - 35% Polyhydramnios

- Ongoing
  - 3%
  - n=3

- IUD
  - 14%
  - (n=15)

- NND
  - 23%
  - (n=25)

- Alive
  - 60%
  - (n=65)

- Alive (n=108)
Neonatal Deaths (NND) n=25

- 8 pulmonary hypoplasia
- 5 PPHN
- 4 Sepsis (2 + Trisomy 21, 1 + Sialidosis)
- 2 NEC (1 + Truncus arteriosus & IUGR++)
- 1 pulmonary lymphangiectasia
- 1 pulmonary hmg.
- 1 IVH grade 4
- 1 DIC, acidosis/shock, HR <40 at birth
- 1 hydropic at birth. No autopsy

5 Genetic Syndromes:
- 2 Noonan
- 1 Klippel-Trenaunay-Weber + brain heterotopia
- 1 Simpson-Golabi-Behmel
- 1 Type II Sialidosis

Pericardial Effusion
Pleural Effusion

CCAM Classification

<table>
<thead>
<tr>
<th>Histological (Stocker)</th>
<th>Ultrasound</th>
</tr>
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<tbody>
<tr>
<td>Type I</td>
<td>Macrocytic</td>
</tr>
<tr>
<td>a few large cysts</td>
<td>single or multiple cysts</td>
</tr>
<tr>
<td>Type II</td>
<td>Microcytic</td>
</tr>
<tr>
<td>multiple small cysts</td>
<td>solid appearance</td>
</tr>
<tr>
<td>Type III</td>
<td>small cysts</td>
</tr>
<tr>
<td>large “solid” masses</td>
<td></td>
</tr>
</tbody>
</table>

Right Atrial Aneurysm
36+5 wks
CCAML (n=134) (1983-97) UCSF & CHOP

- 101 No intervention
- 25 hydropic ALL died (9 “mirror” syndrome)
- 76 no hydrops ALL alive
- ? Role for open fetal sx.


CCAML - Current status

- No hydrops
  - Excellent outcome, regardless of size
  - Expectant management
  - Tertiary care delivery if large
  - Postnatal imaging ± resection
  - U/S measurements (CVR) may stratify risk
  - ?? Role for steroids

- Hydrops
  - Macrocystic — Shunt
  - Microcystic — Deliver Fetal surgery

Fetal Lung Lesions
Expectant Management - Outcome

BPS
- Isolated
  - n=95
  - 96% survival
  - 40% regressed antenatally
  - 3 NND Hydrops + pulmonary hypoplasia
- Hydrops (n=10) → V. poor survival + pulm. hypoplasia

CCAM microcystic
- n=645
- 97.2% survival
- 50% regressed antenatally

Shunting of multilocular CCAM’s + hydrops / hydramnios (n=10)

<table>
<thead>
<tr>
<th>Shunt</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrops</td>
<td>Vacuum 37 wk</td>
</tr>
<tr>
<td>hydrops + hydramnios</td>
<td>SVD 39 wk</td>
</tr>
<tr>
<td>hydramnios</td>
<td>SVD 38 wk</td>
</tr>
<tr>
<td>hydrops</td>
<td>SVD 39 wk</td>
</tr>
<tr>
<td>ascites + hydramnios</td>
<td>SVD 38 wk</td>
</tr>
<tr>
<td>rapidly enlarging</td>
<td>Breech delivery 38 wk</td>
</tr>
<tr>
<td>hydrops, massive lesion</td>
<td>IUD next day</td>
</tr>
<tr>
<td>rapidly enlarging</td>
<td>Shunt dislodged 3 wks later – no recurrence</td>
</tr>
<tr>
<td>hydrops</td>
<td>SVD 37 wk</td>
</tr>
</tbody>
</table>

Lung mass size

<table>
<thead>
<tr>
<th>cm²</th>
<th>weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>25</td>
<td>32</td>
</tr>
</tbody>
</table>

Indications for Fetal Thoracic Shunting

- Large Pleural Effusions
- Macrocystic CCAM’s
- Bronchopulmonary Sequestrations (BPS)
  - Bronchogenic cysts??
  - Pericardial effusions??
- Hydrops
- Polyhydramnios
### Natural history of LUTO

<table>
<thead>
<tr>
<th>Author and year (ref. No.)</th>
<th>Number of cases</th>
<th>Mortality</th>
<th>Cystic renal disease/chronic renal failure</th>
<th>Pulmonary hypoplasia</th>
<th>Associated structural or chromosomal anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al 1985[1-2]</td>
<td>18</td>
<td>33%</td>
<td>56%</td>
<td>30%</td>
<td>56%</td>
</tr>
<tr>
<td>Mahoney et al 1985[3-5]</td>
<td>40</td>
<td>63%</td>
<td>45%</td>
<td>40%</td>
<td>–</td>
</tr>
<tr>
<td>Nakayama et al 1986[6-11]</td>
<td>11</td>
<td>45%</td>
<td>37%</td>
<td>48%</td>
<td>–</td>
</tr>
<tr>
<td>Hayden et al 1988[12]</td>
<td>14</td>
<td>64%</td>
<td>–</td>
<td>36%</td>
<td>43%</td>
</tr>
<tr>
<td>Reuss et al 1988[13]</td>
<td>43</td>
<td>72%</td>
<td>36%</td>
<td>10%</td>
<td>42%</td>
</tr>
<tr>
<td>Anumba et al 2005[14]</td>
<td>113</td>
<td></td>
<td>Prenatal detection before (includes TOP)</td>
<td>24 weeks 67%</td>
<td>Without shunting: 76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Postnatal detection 53%</td>
<td>24 weeks 40%</td>
<td>With shunting: 25%</td>
</tr>
</tbody>
</table>

**Total/mean values**: 239 | 58% | 47% | 31% | 41%

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### LUTO - Shunts

**Long Term Outcome**

<table>
<thead>
<tr>
<th>Detroit 1999</th>
<th>UCSF 2001</th>
<th>Toronto 2001</th>
<th>CHOP 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Followed up</td>
<td>14/21</td>
<td>14/14</td>
<td>9/9</td>
</tr>
<tr>
<td>Alive</td>
<td>62%</td>
<td>57%</td>
<td>67%</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>36%</td>
<td>63%</td>
<td>50%</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>43%</td>
<td>37%</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Normal = GFR > 70 mL/min Failure = Transplant or Dialysis*

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**References**

- Thomas et al 1985
- Mahoney et al 1985
- Nakayama et al 1986
- Hayden et al 1988
- Reuss et al 1988
- Anumba et al 2005
- Freedman AL. *Lancet* 1999;354:374
- McLorie G. *J Urol* 2001;166:1036
- Biard J. *O&G* 2005;106(3):503
Amniotic Fluid Circulation

Mid-trimester PPROM (14-28 wk)
Prediction of Pulmonary Hypoplasia – Meta-analysis

- 0.7% pregnancies
- Mortality: 1-48%
- Different clinical, pathological, methodological definitions:
  - Congen. Pneumonia
  - IRDS
  - Pulm. Hypoplasia
- 28 studies n=1,337
  - GA PPROM
  - Latency
  - Oligohydramnios severity
- Implications: Monitoring in Labour
  - C/S
  - Neonatal Resuscitation

Amnioinfusion for PPROM

- 5 trials. data analysed from 4 studies (n = 241)
- Transcervical amnioinfusion
  - improved cord pH (artery)
  - ↓ variable decelerations in labour (RR 0.52; 95%CI 0.3-0.91)
- Transabdominal amnioinfusion
  - neonatal death (RR 0.3; 95%CI 0.14-0.66)
  - neonatal sepsis (RR 0.26; 95%CI 0.11-0.61)
  - pulmonary hypoplasia (RR 0.22; 95%CI 0.06-0.88)
  - puerperal sepsis (RR 0.2; 95%CI 0.05-0.7)
Amnioinfusion for PPROM

Conclusion

• Results encouraging
• Limited by:
  • sparse data
  • unclear methodological robustness
• Further evidence required before can be recommended for routine clinical practice

Hofmeyr G. Cochrane Library 2011, Issue 12

Fetal Breathing Movements

• FBM important for lung growth
• Spinal cord transection above phrenic nucleus → small lungs
• Bilat. phrenic nerve transection
• ↑ oligohydramnios related pulm hypoplasia due to ↓ FBM
• ↓ pulmonary i/stitial fluid → no stenting → pulm hypoplasia?


Fetal Akinesia Deformation Sequence

“Arthrogryposis”

• Pena, Shokeir 1974, 76
  • IUGR, contractures, pulm hypoplasia, polyhydramnios, dysmorphic facies, short umbilical cord
• Neuropathy
  • Cerebral & cerebellar dysgenesis
  • UMN, LMN
  • Spinalm tract, myelin, end plate disturbances
  • Ischaemia – loss of neural fx.
• Myopathy
• Dermatopathy
• Teratogens
• Extrinsic fetal immobilization – oligohydramnios

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• Teratogens
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MRI in Fetal Akinesia & associated abN

Nemec S. Prenat Diagn 2011; 31: 484–490
Antioxidants in prevention of pulmonary hypoplasia (rats)

- CDH induced by maternal administration of single oral dose of nitrofen on day 9.5 of gestation (133 rats with CDH)
- Vitamin C & E administered prenatally
  - All earlier studies reported that antioxidant vitamins had beneficial effects on pulmonary hypoplasia

Results:
- Vitamin C or E supplementation alone less effective than combined vitamin C & E.
- Histological findings showed that combination of vitamins more effective than vitamin alone groups

Fibroblast growth factor (Fgf8)
Role in lung development (mice)?

- Fgf8 essential for vertebrate cardiovascular, craniofacial, brain & limb development
- Budding, lobation & branching morphogenesis unaffected in early stage Fgf8 hypomorphic & conditional mutant lungs
- Fgf8 may contribute to postnatal alveologenesis.
- Therapeutic implications of identifying factor or pathway that can be targeted to stimulate normal alveolar development

Fetal Conditions Associated with Secondary Lung Hypoplasia

**Intrathoracic**
- CDH
  - *Diaphragmatic eventration?*
- Lung masses
  - CCAM
  - BPS
- Mediastinal/cardiac masses
- Pleural effusions
- Pericardial effusions

**Extrathoracic**
- Oligohydramnios
  - Bilat. renal agenesis
  - Severe renal dysfunction
  - LUTO
  - PPROM
  - “Stuck twin”
- Skeletal dysplasias
  - small thorax
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